Office of
Intellectual Property Counsel

3M

October 10, 1996

#14

Honorable Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Included herewith is an Application for Patent Extension (Attorney's Docket No. F.N. 43853USA1D) of the term of U.S. Patent No. 5,439,670 being filed by Riker Laboratories, Inc. This Application includes an original copy of the Application itself (including the Declaration and Power of Attorney).
Please charge the filing fee of $1090.00 to Deposit Account No. 13-3723. Please charge to Deposit Account No. 13-3723 any additional fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of this application. This authorization includes the fee for any extension of time under 37 CFR 1.136(a) that may be necessary. To the extent any such extension should become necessary it is hereby requested.

Respectfully submitted,

Walter N. Kirn
Registration No. 21,196

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Minnesota Mining and
Manufacturing Company

PO Box 33427
St. Paul, MN 55133-3427 USA
612 733 1500
612 736 3833 Facsimile
29 7023 Telex
PATENTS Cable

PATENT
Docket No. 43853USA1D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 5,439,670

APPLICATION FOR PATENT EXTENSION

EXPRESS MAIL CERTIFICATE

"Express Mail" mailing label number TB784873507US

Date of Deposit: October 11, 1996

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Box Patent Extension, Washington, D. C. 20231.

Mary L. Hoff

3M Office of Intellectual Property Counsel
P. O. Box 33427
St. Paul, Minnesota 55133-3427
(612) 733-1523

Date: October 11, 1996

CERTIFICATION

I hereby certify that this is an original copy of Application for Patent Extension of U.S. Patent No. 5,439,670.

Date: October 10, 1996

Walter N. Kirn

Walter N. Kirn
Registration No. 21,196

State of Minnesota)
) ss
County of Ramsey)

On this 10th day of October, 1996, before me personally appeared the above-named Walter N. Kirn personally known to me, and known by me to be the person described in and who executed the foregoing instrument, and who acknowledged that he executed the same as his free act and deed, on the day and year aforesaid.

MARY L. HOFF
NOTARY PUBLIC - MINNESOTA
WASHINGTON COUNTY
My Comm. Expires Jan. 31, 2000

Mary L. Hoff

Notary Public

PATENT
Docket No. 43853USA1D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 5,439,670

APPLICATION FOR PATENT EXTENSION

EXPRESS MAIL CERTIFICATE

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Mary L. Hoff

3M Office of Intellectual Property Counsel
P. O. Box 33427
St. Paul, Minnesota 55133-3427
(612) 733-1523

Date: October 11, 1996

Office of
Intellectual Property Counsel

3M

October 10, 1996

Honorable Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Included herewith is an Application for Patent Extension (Attorney's Docket No. F.N. 43853USA1D) of the term of U.S. Patent No. 5,439,670 being filed by Riker Laboratories, Inc. This Application includes an original copy of the Application itself (including the Declaration and Power of Attorney).
Please charge the filing fee of $1090.00 to Deposit Account No. 13-3723. Please charge to Deposit Account No. 13-3723 any additional fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of this application. This authorization includes the fee for any extension of time under 37 CFR 1.136(a) that may be necessary. To the extent any such extension should become necessary it is hereby requested.

Respectfully submitted,

Walter N. Kirn
Registration No. 21,196

TKR\mlh
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PO Box 33427
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612 733 1500
612 736 3833 Facsimile
29 7023 Telex
PATENTS Cable

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 5,439,670

POWER OF ATTORNEY

Honorable Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D. C. 20231

Sir:

RIKER LABORATORIES, INC., the owner of U.S. Patent No. 5,439,670, by a written assignment recorded on November 21, 1989, and found at Reel 5187, Frame 599, hereby appoints Gary L. Griswold (Reg. No. 25,396), Walter N. Kirn (Reg. No. 21,196), Terryl K. Qualey (Reg. No. 25,148), Warren R. Bovee (Reg. No. 26,434), Gerald F. Chernivec (Reg. No. 26,537), Douglas B. Little (Reg. No. 28,439), David R. Cleveland (Reg. No. 29,524), and Ted K. Ringsred (Reg. No. 35,658) as attorneys with full powers (including the powers of appointment, substitution and revocation) to prosecute the APPLICATION FOR PATENT EXTENSION of U.S. Patent No. 5,439,670 being filed by RIKER LABORATORIES, INC., and to transact all business in the Patent and Trademark Office and the Department of Health and Human Services in connection therewith. The mailing address and the telephone number of the above-mentioned attorneys is:

3M/Office of Intellectual Property Counsel
P.O. Box 33427
St. Paul, Minnesota 55133-3427
Telephone: (612) 733-1500

RIKER LABORATORIES, INC.

By: JoAnn J. Bohne
JoAnn J. Bohne
Assistant Secretary

DATED: Oct. 10, 1996

TKR\mlh
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PATENT

Docket No. 43853USA1D

DECLARATION UNDER 37 CFR 1.740(a)(17)

This Application is submitted pursuant to extension of the term of U.S. Patent No. 5,439,670. The undersigned, as agent for Riker Laboratories, Inc., the owner of said patent, hereby declares:

THAT I have reviewed and understand the contents of the attached application papers consisting of a 20 page Application and Exhibits A, B, C, D, E and F thereto;

THAT I believe U.S. Patent No. 5,439,670 is subject to extension pursuant to 36 U.S.C. 156 and 37 CFR § 1.710;

THAT I believe an extension of 40 days is fully justified under 35 U.S.C. 156;

THAT I believe U.S. Patent No. 5,439,670 meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. 156 and 37 CFR § 1.720; and

THAT all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 5,439,670.

DATE: Oct. 10, 1996

Walter N. Kirn

Walter N. Kirn
Registration No. 21,196

TKR\mlh
P:\FEULNGRE\PTE\DECLARA.DOC

PATENT
Docket No. 43853USA1D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 5,439,670

APPLICATION FOR PATENT EXTENSION

Honorable Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Applicant, Riker Laboratories, Inc., hereby applies for extension of the term of U. S. Patent No. 5,439,670. A power of attorney in favor of the undersigned is submitted herewith.

BACKGROUND

This application for patent extension concerns U.S. Patent No. 5,439,670. Riker Laboratories, Inc. is the owner of U.S. Patent No. 5,439,670, the written assignment being recorded on November 21, 1989, and found at Reel 5187, Frame 599. The 3M Pharmaceuticals division of the Minnesota Mining and Manufacturing Company (3M) has applied for and obtained Food and Drug Administration (FDA) approval for the commercial marketing of albuterol sulfate inhalation aerosol. This product is claimed in U.S. Patent No. 5,439,670. Salbutamol sulfate, an INN name, is used in U.S. Patent 5,439, 670 while the USAN name for the same chemical, albuterol sulfate, is used in the documents sent to the Food and Drug Administration for product approval.

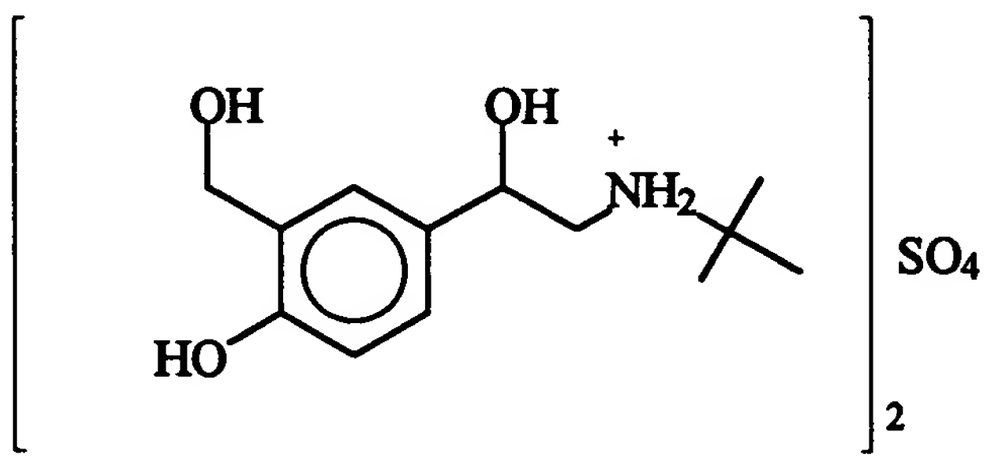
ELIGIBILITY

U.S. Patent No. 5,439,670 is eligible for extension under the provisions of 35 U.S.C. § 156(a) and 37 CFR § 1.720. U.S. Patent No. 5,439,670 has not expired, and the term of the patent has never been extended. No other United States Patent has been extended based on the review period for albuterol sulfate inhalation aerosol. U.S. Patent 5,439,670 claims the product, albuterol

sulfate in propellant HFA-134a (1,1,1,2-tetrafluoroethane), ethanol, and oleic acid. The approved product was subject to a regulatory review period as defined in 35 U.S.C. § 156(g)(1). The product has not previously been approved for commercial marketing in the United States. This application for patent term extension is being submitted within the time limit specified in 35 U.S.C. § 156(d)(1).

APPLICATION (37 CFR 1.740(a))

(1) The approved product is an inhalation aerosol for the treatment or prevention of bronchospasm in patients with reversible obstructive airway disease. The chemical composition for albuterol sulfate inhalation aerosol comprises: 1,1,1,2 tetrafluoroethane, ethanol, oleic acid, and albuterol sulfate. The active ingredient being albuterol sulfate. The tradename for albuterol sulfate inhalation aerosol approved by the FDA is PROVENTIL® HFA. Albuterol sulfate has the following structure:



(2) The Federal statute under which the regulatory review occurred for albuterol sulfate inhalation aerosol is § 505(b) of the Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)).

(3) Albuterol sulfate inhalation aerosol presented as PROVENTIL® HFA was approved by the FDA under § 505(b) of the Federal Food, Drug and Cosmetic Act on August 15, 1996, for commercial marketing and use as a drug product for the treatment or prevention of bronchospasm in patients with reversible obstructive airway disease. A copy of an approved Package Insert for PROVENTIL® HFA, wherein all sections thereof are reproduced on several pages, is attached hereto as Exhibit A. The approved route of administration is oral.

(4) The active ingredient of PROVENTIL® HFA is albuterol sulfate. Albuterol sulfate has been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act. To the best of the applicant's knowledge, the uses for which albuterol sulfate has been approved are aerosol inhalation aerosols (combination of ingredients different than present aerosol inhalation), an inhalation solution, and an oral syrup. Attached is hereto as Exhibit B is a drug product list from the Approved Drug Products With Therapeutic Evaluation , Public Health Service, FDA.

(5) This application for patent extension is being submitted within the sixty day period permitted for submission as provided in 35 U.S.C. § 156(d)(1), the last day on which the application could be submitted being October 13, 1996.

(6) The subject of this application for patent extension is U.S. Patent No. 5,439,670 which issued on August 8, 1995 and expires on July 6, 2010. A portion of the term of this patent subsequent to July 6, 2010 has been disclaimed. The inventors named in this patent are Tarlochan S. Purewal and David J. Greenleaf. U.S. Patent No. 5,439,670 issued on a continuation of U.S. S.N. 07/649,140 which is a continuation of U.S. S.N. 07/442,119 abandoned on November 28, 1989. U.S. S.N. 07/649,140 issued as U.S. Patent No. 5,225,183, and contains claims reading on a genus of inhalation aerosols of which albuterol sulfate inhalation aerosol is a species. U.S. Patent No. 5,225,183 has not been extended and is not the subject of an application for patent extension.

(7) A copy of U.S. Patent No. 5,439,670 is attached hereto as Exhibit C. At the present time, no receipt of maintenance fee payment or reexamination certificate has issued in U.S. Patent No. 5,439,670. A portion of the term of patent 5,439,670 subsequent to July 6, 2010 has been disclaimed. A certificate of correction for patent 5,439,670 is concurrently being filed.

(8) A copy of the document disclaiming the term of patent 5,439,670 subsequent to July 6, 2010 has been attached hereto as Exhibit D. A copy of the certificate of correction has been attached as Exhibit E.

(9) U.S. Patent No. 5,439,670 claims the approved product, albuterol sulfate inhalation aerosol. Claims 1-4, 6-18, and 20-28 all read on the chemical composition of the product. Specifically, claim 1 provides the general composition of the product, a propellant (1,1,1,2-tetrafluoroethane) a surface active agent (oleic acid), and a compound having a higher polarity than 1,1,1,2-tetrafluoroethane (ethanol). Claim 2, which depends on claim 1, further defines the compound having a higher polarity than 1,1,1,2-tetrafluoroethane as including ethanol. Claim 3, which depends on claim 1, characterizes the method of administration of the aerosol formulation to the patient to be oral inhalation. Claim 4, dependent on claim 3, characterizes the drug to be in a suspension (particles) and identifies the size of the particles. Claim 6-10 , which are dependent on claim 3, characterize the quantity of 1,1,1,2-tetrafluoroethane and the compound of higher polarity (ethanol) in the product. Claim 11, which depends on claim 3, characterizes the surface active agent as including oleic acid. Claim 12, which depends on claim 3, further defines the quantity of surface active agent and drug within the product. Claim 13, which depends on claim 3, further characterizes the drug of the formulation as including salbutamol (albuterol sulfate). Claim 14, which depends on claim 3, further characterizes the quantity of drug in the aerosol formulation. Claim 15 is a second independent claim that characterizes the general composition of the product, a propellant (1,1,1,2-tetrafluoroethane) a surface active agent (oleic acid), and a compound having a higher polarity than 1,1,1,2-tetrafluoroethane (ethanol). Claim 16, which depends on claim 15, further defines the compound having a higher polarity than 1,1,1,2-tetrafluoroethane as including ethanol. Claim 17, which depends on claim 15, characterizes the method of administration of the aerosol formulation to the patient to be oral inhalation. Claim 18, dependent on claim 15, characterizes the drug to be in a suspension (particles) and identifies the size of the particles. Claim 20-24 , which are dependent on claim 15, characterize the quantity of 1,1,1,2-tetrafluoroethane and the compound of higher polarity (ethanol) in the product. Claim 25, which depends on claim 15, characterizes the surface active agent as including oleic acid. Claim 26, which depends on claim 15, further defines the quantity of surface active agent and drug within the product. Claim 27, which depends on claim 15, further characterizes the drug of the formulation as including salbutamol (albuterol sulfate). Claim 28, which depends on claim 15, further characterizes the quantity of drug in the aerosol formulation.

(10) An Investigational New Drug application (IND) for albuterol sulfate inhalation aerosol was submitted to the Food and Drug Administration (FDA), Division of Oncology and Pulmonary Drug Products (HFD-150) on April 22, 1992. The IND (# 39,502) was recorded in the FDA on April 27, 1992, as an exemption under subsection (i) of § 505 of the Food, Drug and Cosmetic Act (21 U.S.C. § 355 (I)) and the exemption became effective on May 28, 1992, a date subsequent to the date the exemption under Subsection (I) of § 505 became effective. A New Drug Application (NDA, #20-503) on albuterol sulfate inhalation aerosol was filed by 3M Pharmaceuticals under § 505 (b) of the Food, Drug and Cosmetic Act (21 U.S.C. § 355 (b)) on May 15, 1995 (After a pre-NDA meeting held on May 11, 1994 and a refusal to file meeting held on February 13, 1996 at which an agreement was reached). The NDA was accepted on July 17, 1995.

(11) A brief description of activities undertaken by the Applicant during the applicable regulatory review period with respect to albuterol sulfate inhalation aerosol and the significant dates applicable to such activities are as follows:

Inhalation Tolerance Study in dogs (#0790RD0449) was completed November 26, 1990 and the report was issued March 25, 1992.

A 28-Day Inhalation Study in dogs (#0790SD0450) was conducted January 21, 1991 through February 21, 1991. The report was issued March 24, 1992.

Preliminary Inhalation Tolerance Study in dogs (#0790RR0451) was conducted March 12, 1991 through March 18, 1991. The report was issued March 24, 1992.

A 28-Day Inhalation Study in Rats (#0790SR0452) was conducted March 29, 1991 through April 29, 1991. The report was issued March 24, 1992.

Clinical Study SL34--PB-01-91-GB-l was conducted and the final report was issued December 1991.

IND 39,502 was submitted on April 22, 1992. It was logged in at the FDA on April 27, 1992 and became effective on May 27, 1992.

Clinical Study 0034-PB-01-91-GB-1 was conducted September 3, 1991 through October 1, 1991. The report was issued March 1993.

A 90-Day Inhalation Study in Rats (#0792SR0170) was conducted April 30, 1992 through August 14, 1992. The report was issued July 1993.

Clinical Study SL34-PB-04-91-GB-XX was conducted April 2, 1992 through November 23, 1992. The report was issued April 13, 1993.

Clinical Study 1007-SILV was conducted June 9, 1992 through August 11, 1992. The report was issued June 1993.

Clinical Study 1031-SILV was conducted from September 24, 1992 through December 15, 1992. The report was issued April 1993.

A Nose only Inhalation study in rats (#0792TR01710) was conducted and the report issued June 22, 1993.

Clinical Study 1038-SILV was conducted from December 27, 1992 though April 21, 1993. The report was issued April 21, 1994.

Clinical Study 1044-SILV was conducted from May 10, 1993 through September 29, 1993. The report was issued April 27, 1994.

Clinical Study 1012-SILV was conducted from June 1993 through April 1994. The report was issued August 26, 1994.

Clinical Study 1037-SILV was conducted from July 15, 1993 through October 22,1993. The report was issued April 20, 1994.

Clinical Study 1091-SILV was conducted from September 23, 1993 through January 10, 1994. The report was issued April 5, 1995.

A Inhalation feasibility study in dogs (#0790AD0448) was conducted from October 12, through October 20, 1993. The report was issued March 24, 1992.

Clinical Study 1106 was conducted from October 1993 through April 1995. The report was issued August 22, 1995.

Clinical Study 1011-SILV was conducted from March 21, 1993 through April 9, 1994. The report was issued June 29, 1994.

Pre-NDA meeting May 11, 1994.

Clinical Study 1145-SILV was conducted from August 29, 1994 through December 1, 1994. The report was issued May 1, 1995.

Clinical Study 1154-SILV was conducted from September 1994 through December 1995. The report was issued May, 17, 1996.

NDA presubmission of Chemistry, Manufacturing and Control Section submitted July 1, 1994.

NDA date of application October 14, 1994.

Acknowledgment from FDA on receipt of application, October 18, 1994.

December 15, 1994 refusal to file letter from FDA.

A 90 Day Inhalation Toxicology study in dogs (#0795SD00174) was conducted May 3, 1995 through June 6, 1995. The report was issued June 1996.

CMC deficiency letter from FDA dated May 10, 1995.

NDA refile submitted May 15, 1995.

NDA refile accepted July 17, 1995.

Amendment 8, CMC deficiency response submitted August 18, 1995 (response to FDA's May 10, 1995 deficiency letter).

FDA clinical comments 9/7/95.

FDA environmental assessment deficiency letter dated 8/30/95.

Amendment 11, submission on 10/31/95 of responses to FDA question of September 28, 1995, regarding the August 8, 1995 submission.

Amendment 12, submission on 11/1/95 response to FDA clinical comments dated 9/7/95.

Environmental assessment deficiency letter from FDA on 4/16/96.

CMC deficiency letter received from the FDA on 3/14/96.

Amendment 25, submission on 4/29/96, response to FDA letter of 3/14/96.

March 20, 1996 FDA Advisory Committee Meeting.

Amendment 29, submission on May 3, 1996. Response to FDA letter of 4/16/96.

CMC deficiency letter from FDA dated August 7, 1996.

Amendment 41, submission on 8/9/96 response to FDA deficiency letter dated August 7, 1996.

Amendment 42, submission on 8/14/96 of methods validation package.

Amendment 46, submission on 8/14/96 on final labeling with changes requested by FDA.

Amendment 49, submission on 8/13/96 clarification of CMC questions (This is the last amendment prior to approval).

The NDA was approved August 15, 1996.

(12) In the opinion of the Applicant, U.S. Patent No. 5,439,670 is eligible for an extension of term. The extension claimed herein is 40 days which is the maximum allowed for albuterol sulfate inhalation aerosol under 35 USC § 156 (g)(1) and 35 USC § 156 (c). The applicable review period for albuterol sulfate inhalation aerosol actually exceeds 40 days, as calculated as follows:

The period set forth in 35 U.S.C. § 156 (g)(1)(B)(i) begins from the date an exemption under subsection (i) of § 505 became effective (May 28, 1992) to the date the NDA was submitted (May 15, 1995). The period set forth in 35 U.S.C. § 156(g)(1)(ii) is from the date of the NDA was submitted, May 15, 1995 to the date the NDA was approved, August 15, 1996. However, under 35 U.S.C. § 156 (c), the term of a patent eligible for extension shall be extended by the time equal to the regulatory review period for the approved product which period occurs after the date the patent is issued. The term of the patent eligible for extension is calculated from the issue date of U.S. Patent No. 5,439,670 Aug. 8, 1995 to the date the NDA was approved (August 15, 1996), 373 days. However, because of the fourteen-year cap imposed by 35 U.S.C. 156 (c)(3), the total amount of extension is 40 days. This period is the number of days between August 15, 2010 (fourteen years added on to the date the NDA was approved) and July 6, 2010 (U.S. Patent No. 5,439,670 has disclaimed the portion of the patent past July 6, 2010).

(13) The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to this application for patent extension.

(14) Please charge the filing fee of $1090.00 to Deposit Account No. 13-3723. Please charge to Deposit Account No. 13-3723 any additional fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of this application. This authorization includes the fee for any extension of time under 37 CFR 1.136(a) that may be necessary. To the extent any such extension should become necessary it is hereby requested. A declaration meeting the requirements of the guidelines is attached.

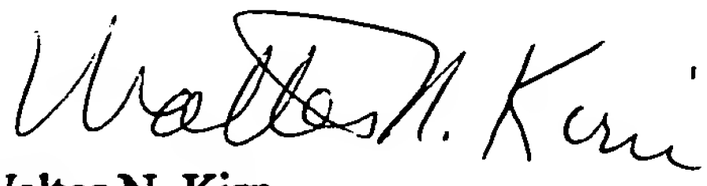
(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed to are:

Ted K. Ringsred
3M/Office of Intellectual Property Counsel
P.O. Box 33427
St. Paul, MN 55133-3427
(612) 736-5839

(16) A duplicate of the application papers, certified as such are attached hereto as Exhibit F.

In view of the above, it is believed that U.S. Patent No. 5,439,670 is entitled to an extension of 40 days. An official notice to that effect in the form of a certificate of extension is courteously requested.

Respectfully submitted,



Walter N. Kirn
Registration No. 21,196

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EXHIBIT A

F-19247309

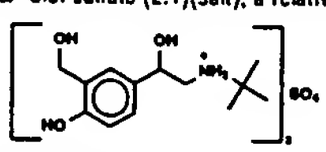
PROVENTIL® HFA (Albuterol Sulfate Inhalation Aerosol)

607700

FOR ORAL INHALATION ONLY

Prescribing Information

DESCRIPTION The active component of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) is albuterol sulfate, USP racemic α¹-[(*tert*-Butylamino)methyl]-4-hydroxy-m-xylene-α, α¹-diol sulfate (2:1)(salt), a relatively selective beta$_2$-adrenergic bronchodilator.



Albuterol sulfate is the official generic name in the United States. The World Health Organization recommended name for the drug is salbutamol sulfate. The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white to off-white crystalline solid. It is soluble in water and slightly soluble in ethanol. PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) is a pressurized metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1,1,1,2-tetrafluoroethane), ethanol, and oleic acid.

Each actuation delivers 120 mcg albuterol sulfate, USP from the valve and 108 mcg albuterol sulfate, USP from the mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece). Each canister provides 200 inhalations (pharmacy pack) or 100 inhalations (hospital pack).

This product does not contain chlorofluorocarbons (CFCs) as the propellant.

CLINICAL PHARMACOLOGY

Mechanism of Action *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, recent data indicate that there is a population of beta$_2$ receptors in the human heart which comprise between 10% and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors, however, is not yet established. (See **WARNINGS** for **Cardiovascular Effects.**)

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3',5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

Albuterol has been shown in most clinical trials to have more bronchial smooth muscle relaxation effect than isoproterenol at comparable doses while producing fewer cardiovascular effects. However, all beta-adrenergic drugs, including albuterol sulfate, can produce a significant cardiovascular effect in some patients.

Preclinical Intravenous albuterol studies in rats have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to about 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), the drug achieves concentrations of more than 100 times those in whole brain.

Studies in pregnant rats with tritiated albuterol have demonstrated that approximately 10% of the circulating maternal drug is transferred to the fetus. Disposition in fetal lungs is comparable to maternal lungs, but fetal liver disposition is 1% of maternal liver levels.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when ß-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is unknown.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380 - 1300 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related chlorofluorocarbons (CFCs), which have been used extensively in metered dose inhalers.

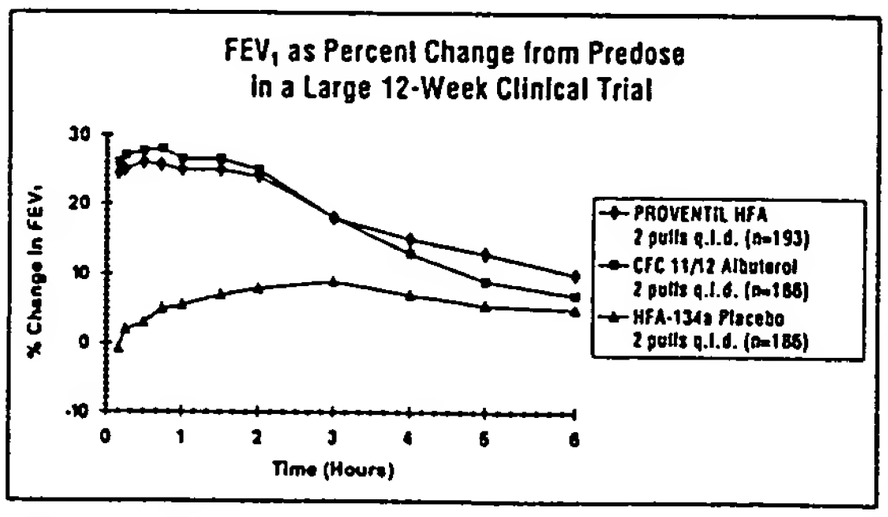
In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3-27 minutes in animals and 5-7 minutes in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both extremely short leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

Pharmacokinetics In a single-dose bioavailability study which enrolled 6 healthy, male volunteers, transient low albuterol levels (close to the lower limit of quantitation) were obtained after administration of two puffs from both PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) and a CFC 11/12 propelled albuterol inhaler. No formal pharmacokinetic analyses were possible for either treatment, but systemic albuterol levels appeared similar.

Clinical Trials In a 12-week, randomized, double-blind, double-dummy, active- and placebo-controlled trial, 565 patients with asthma were evaluated for the bronchodilator efficacy of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) (193 patients) in comparison to a CFC 11/12 propelled albuterol inhaler (186 patients) and an HFA-134a placebo inhaler (186 patients).

Serial FEV$_1$ measurements (shown below as percent change from test-day baseline) demonstrated that two inhalations of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) produced significantly greater improvement in pulmonary function than placebo and produced outcomes which were clinically comparable to a CFC 11/12 propelled albuterol inhaler.

The mean time to onset of a 15 percent increase in FEV$_1$ was 6 minutes and the mean time to peak effect was 50 to 55 minutes. The mean duration of effect as measured by a 15 percent increase in FEV$_1$ was 3 hours. In some patients, duration of effect was as long as 6 hours.



INDICATIONS AND USAGE PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) is indicated for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS

1. **Paradoxical Bronchospasm:** Inhaled albuterol sulfate can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.
2. **Deterioration of Asthma:** Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, eg, corticosteroids.
3. **Use of Anti-Inflammatory Agents:** The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, eg, corticosteroids, to the therapeutic regimen.
4. **Cardiovascular Effects:** PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol), like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol), like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5. **Do Not Exceed Recommended Dose:** Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.
6. **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

PRECAUTIONS

General Preparations containing sympathomimetic amines such as albuterol sulfate should be used with caution in patients who are unusually responsive to such agents and in patients with convulsive disorders, hyperthyroidism, or diabetes.

Beta-adrenergic-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for Patients See illustrated Patient's Instructions for Use. SHAKE WELL BEFORE USING. Patients should be given the following information:

The action of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) should last up to 4 to 6 hours. PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) should not be used more frequently than recommended. Do not increase the number of puffs or frequency of doses of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) without consulting your physician. If you find that treatment with PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, medical attention should be sought immediately. While you are taking PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol), other inhaled drugs should be taken only as directed by your physician. If you are pregnant or nursing, contact your physician about use of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol).

Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Effective and safe use of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) includes an understanding of the way that it should be administered. Use PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) only with the actuator supplied with the product. Discard the canister after 200 sprays have been used. (See Patient's Instructions for Use.)

Drug Interactions

1. **Beta Blockers:** Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta agonists, such as PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol), but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta blockers. However, under certain circumstances, eg, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic-blocking agents in patients with asthma. In this setting, cardioselective beta blockers could be considered, although they should be administered with caution.
2. **Diuretics:** The ECG changes and/or hypokalemia which may result from the administration of nonpotassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta agonists, especially when the recommended dose of the beta agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta agonists with nonpotassium sparing diuretics.
3. **Digoxin:** Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear; however, careful evaluation of serum digoxin levels is recommended in patients who are currently receiving digoxin and albuterol.
4. **Monoamine oxidase inhibitors or tricyclic antidepressants:** PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2-year study in rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at oral dietary doses of 2, 10, and 50 mg/kg/day (approximately 12, 60, and 300 times the maximum recommended human daily inhalation dose on a mg/m² basis). In another study this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice at dietary doses up to 500 mg/kg/day (approximately 1560 times the maximum recommended human daily inhalation dose on a mg/m² basis) revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis or impaired fertility in rats at oral doses up to 50 mg/kg (approximately 300 times the maximum recommended human daily inhalation dose on a mg/m² basis).

Teratogenic Effects - Pregnancy Category C

Albuterol has been shown to be teratogenic in mice. A reproduction study in CD-1 mice given albuterol sulfate subcutaneously (0.025, 0.25, and 2.5 mg/kg) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (approximately equal to the maximum recommended human daily inhalation dose on a mg/m² basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 10 times the maximum recommended human daily inhalation dose on a mg/m² basis). None was observed at 0.025 mg/kg (approximately one tenth the maximum recommended human daily inhalation dose on a mg/m² basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study with oral albuterol in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg (approximately 600 times the maximum recommended human daily inhalation dose on a mg/m² basis).

In a separate inhalation reproduction study in rats using albuterol sulfate/HFA-134a formulation, albuterol sulfate did not exhibit any teratogenic effects at 10.5 mg/kg/day (approximately 65 times the maximum recommended human daily inhalation dose on a mg/m² basis).

There are, however, no adequate and well-controlled studies of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) or albuterol sulfate in pregnant women. Because animal reproduction studies are not always predictive of human response, PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies cannot be established.

Use in Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Nursing Mothers

Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) are excreted in human milk.

Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when albuterol sulfate is administered to a nursing woman.

Pediatrics

The safety and effectiveness of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) in children below the age of 12 years have not been established.

Geriatrics

PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) has not been studied in a geriatric population. As with other $beta_2$-agonists, special caution should be observed when using PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug.

ADVERSE REACTIONS Adverse reaction information concerning PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) is derived from a 12-week, double-blind, double-dummy study which compared PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol), a CFC 11/12 propelled albuterol inhaler, and an HFA-134a placebo inhaler in 565 asthmatic patients. The following table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) treatment group and more frequently in the PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) treatment group than in the placebo group. Overall, the incidence and nature of the adverse reactions reported for PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) and a CFC 11/12 propelled albuterol inhaler were comparable.

Adverse Experience Incidences (% of patients) in a Large 12-week Clinical Trial*

Body System/ Adverse Event (Preferred Term)		PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) (N = 193)	CFC 11/12 Propelled Albuterol Inhaler (N = 186)	HFA-134a Placebo Inhaler (N = 186)
Application Site Disorders	Inhalation Site Sensation	6	9	2
	Inhalation Taste Sensation	4	3	3
Body as a Whole	Allergic Reaction/Symptoms	6	4	< 1
	Back Pain	4	2	3
	Fever	6	2	5
Central and Peripheral Nervous System	Tremor	7	8	2
Gastrointestinal System	Nausea	10	9	5
	Vomiting	7	2	3
Heart Rate and Rhythm Disorder	Tachycardia	7	2	< 1
Psychiatric Disorders	Nervousness	7	9	3
Respiratory System Disorders	Respiratory Disorder (unspecified)	6	4	5
	Rhinitis	16	22	14
	Upper Resp Tract Infection	21	20	18
Urinary System Disorder	Urinary Tract Infection	3	4	2

*This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) group and more frequently in the PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) group than in the HFA-134a placebo inhaler group.

Adverse events reported by less than 3% of the patients receiving PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol), and by a greater proportion of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) patients than placebo patients, which have the potential to be related to PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) include: dysphonia, increased sweating, dry mouth, chest pain, edema, rigors, ataxia, leg cramps, hyperkinesia, eructation, flatulence, tinnitus, diabetes mellitus, anxiety, depression, somnolence, rash. Palpitation and dizziness have also been observed with PROVENTIL HFA.

In small, cumulative dose studies, tremor, nervousness, and headache appeared to be dose related.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of inhaled albuterol. In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, insomnia, headache, and drying or irritation of the oropharynx.

OVERDOSAGE The expected symptoms with overdosage are those of excessive beta stimulation and/or occurrence or exaggeration of any of the symptoms listed under **ADVERSE REACTIONS**, eg, seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol).

The oral median lethal dose of albuterol sulfate in mice and rats was greater than 2,000 mg/kg (approximately 6,000 and 12,000 times the maximum recommended human daily inhalation dose, respectively, on a mg/m² basis). The inhalation median lethal dose could not be determined.

Treatment consists of discontinuation of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol).

DOSAGE AND ADMINISTRATION For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 12 years and older is 2 inhalations repeated every 4 to 6 hours. More frequent administration or a larger number of inhalations is not recommended. In some patients, 1 inhalation every 4 hours may be sufficient. Each actuation of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouthpiece.

HOW SUPPLIED PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) is supplied as a pressurized aluminum canister with a yellow plastic actuator and orange dust cap. Each actuation delivers 120 mcg of albuterol sulfate from the valve and 108 mcg of albuterol sulfate from the mouthpiece (equivalent to 90 mcg of albuterol base). Canisters with a labeled net weight of 6.7 g contain 200 inhalations (NDC 0085-1132-01).

CAUTION **Federal law prohibits dispensing without prescription. Store between 15° and 25°C (59° and 77°F). For best results, canister should be at room temperature before use.**

SHAKE WELL BEFORE USING

PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) should be used only with the actuator provided. The actuator should not be used with other aerosol medications.

Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Exposure to temperatures above 120°F may cause bursting. Keep out of reach of children.

PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) does not contain chlorofluorocarbons (CFCs) as the propellant.

Developed and Manufactured by
3M Pharmaceuticals
Northridge, CA 91324

for

Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033 USA

Rev. 8/96

B-19247309

PROVENTIL® HFA (Albuterol Sulfate Inhalation Aerosol)

Patient's Instructions For Use

Attention Pharmacist: Detach "Patient's Instructions for Use" from package insert and dispense with the product.

607700

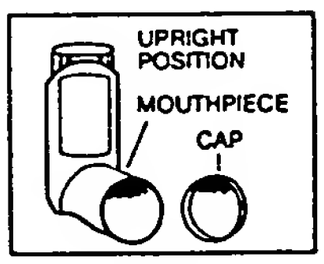


Figure 1

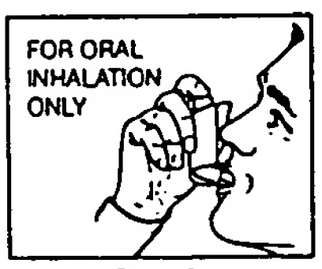


Figure 2

Before using your PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol), read complete instructions carefully.

Please note that CFC indicates that this inhalation aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

1. SHAKE THE INHALER WELL immediately before each use. Then remove the cap from the mouthpiece (see Figure 1). Check mouthpiece for foreign objects prior to use. Make sure the canister is fully inserted into the actuator.

2. BREATHE OUT FULLY THROUGH THE MOUTH, expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth holding the inhaler in its upright position (see Figure 2) and closing the lips around it.

3. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER with your index finger (see Figure 2).

4. HOLD YOUR BREATH AS LONG AS POSSIBLE, up to 10 seconds. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.

5. If your physician has prescribed additional puffs, wait 1 minute, shake the inhaler again and repeat steps 2 through 4. Replace the cap after use.

6. KEEPING THE PLASTIC MOUTHPIECE CLEAN IS EXTREMELY IMPORTANT TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE. To clean, remove the canister and mouthpiece cap. Wash the mouthpiece through the top and bottom with HOT running water at least once a week. Never immerse the metal canister in water. To dry, shake off excess water and let the mouthpiece air dry overnight, then replace the canister and mouthpiece cap. Using the mouthpiece before it is thoroughly dry can cause medication build-up or blockage.

   If it is necessary to use your inhaler immediately after cleaning, shake off excess moisture, replace the canister, and test spray twice into the air, away from your face, to remove remaining water from inside the mouthpiece. Then take your dose as prescribed. At this time, re-wash the mouthpiece, following the instructions above.

7. As with all aerosol medications, it is recommended to test the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks. Test by releasing four "test sprays" into the air, away from your face.

8. PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) will deliver at least 200 sprays. However, after 200 sprays, the amount of drug delivered per spray may not be consistent. You should keep track of the number of sprays used from each canister of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) and discard the canister after 200 sprays.

You may notice a slightly different taste or spray force than you are used to with PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol), compared to other albuterol inhalation aerosol products.

DOSAGE:
Use only as directed by your physician.

WARNINGS:
The action of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) should last up to 4 to 6 hours. PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) should not be used more frequently than recommended. Do not increase the number of puffs or frequency of doses of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) without consulting your physician. If you find that treatment with PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, medical attention should be sought immediately. While you are taking PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol), other inhaled drugs should be taken only as directed by your physician. If you are pregnant or nursing, contact your physician about the use of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol).

Common adverse effects of treatment with PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) include palpitations, chest pain, rapid heart rate, tremor, or nervousness. Effective and safe use of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) includes an understanding of the way that it should be administered. Use PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) only with the actuator supplied with the product. The PROVENTIL HFA actuator should not be used with other aerosol medications.

For best results use at room temperature. Avoid exposing product to extreme heat and cold.

Shake well before use.

Contents Under Pressure.
Do not puncture. Do not store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Store between 15° and 25°C (59° and 77°F). Avoid spraying in eyes. Keep out of reach of children.

Further Information: Your PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) does not contain chlorofluorocarbons (CFCs) as the propellant. Instead the inhaler contains a hydrofluoroalkane (HFA-134a) as the propellant.

Developed and Manufactured by
3M Pharmaceuticals
Northridge, CA 91324

for

Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033 USA

Rev. 8/96 19247309

U.S. Patent 5,225,183

EXHIBIT B

ADENOSINE

INJECTABLE; INJECTION
ADENOSCAN
+ MEDCO RES — 3MG/ML — N20059 001 MAY 18, 1995

ALBUTEROL

AEROSOL, METERED; INHALATION
ALBUTEROL
> ADD > > ADD > AB NORTON WATERFORD — 0.09MG/INH — N73272 001 DEC 28, 1995
> ADD >
VENTOLIN
> DLT > AH GLAXO — 0.09MG/INH — N18473 001
> ADD > AB + GLAXO WELLCOME — 0.09MG/INH — N18473 001

ALBUTEROL SULFATE

SOLUTION; INHALATION
ALBUTEROL SULFATE
> ADD > > ADD > AH BARRE — EQ 0.083% BASE — N73533 001 SEP 26, 1995
> DLT > > DLT > AH BARR — EQ 0.083% BASE — N73533 002 SEP 26, 1995

SYRUP; ORAL
ALBUTEROL SULFATE
AA BARRE — EQ 2MG BASE/5ML — N74454 001 SEP 25, 1995

ALENDRONATE SODIUM

TABLET; ORAL
FOSAMAX
MERCK — EQ 10MG BASE — N20560 001 SEP 29, 1995
+ — EQ 40MG BASE — N20560 002 SEP 29, 1995

ALPRAZOLAM

TABLET; ORAL
ALPRAZOLAM
AB CHELSEA LABS — 0.25MG — N74456 001 AUG 31, 1995

ALPRAZOLAM

TABLET; ORAL
ALPRAZOLAM
AB CHELSEA LABS — 0.5MG — N74456 002 AUG 31, 1995
AB — 1MG — N74456 003 AUG 31, 1995
> ADD > > ADD > AB GENEVA PHARMS — 0.25MG — N74112 001 DEC 29, 1995
> ADD > AB — 0.5MG — N74112 002 DEC 29, 1995
> ADD > > ADD > AB — 1MG — N74112 003 DEC 29, 1995

ALPROSTADIL

INJECTABLE; INJECTION
CAVERJECT
UPJOHN — 0.01MG/VIAL — N20379 001 JUL 06, 1995
+ — 0.02MG/VIAL — N20379 002 JUL 06, 1995

ALSEROXYLON

TABLET; ORAL
RAUWILOID
> DLT > AH — 2MG — N08867 001
• — 2MG — N08867 001

AMANTADINE HYDROCHLORIDE

SYRUP; ORAL
AMANTADINE HCL
AA PHARM ASSOC — 50MG/5ML — N74509 001 JUL 17, 1995

> ADD > AMIFOSTINE

INJECTABLE; INJECTION
ETHYOL
> ADD > > ADD > > ADD > > ADD > + US BIOSCIENCE — 500MG/VIAL — N20221 001 DEC 08, 1995

EXHIBIT C

US005439670A

United States Patent [19]

Purewal et al.

[11] Patent Number: 5,439,670

[45] Date of Patent: * Aug. 8, 1995

[54] MEDICINAL AEROSOL FORMULATIONS

[75] Inventors: **Tarlochan S. Purewal**, Leamington Spa; **David J. Greenleaf**, Loughborough, both of England

[73] Assignee: **Riker Laboratories, Inc.**, St. Paul, Minn.

[*] Notice: The portion of the term of this patent subsequent to Jul. 6, 2010 has been disclaimed.

[21] Appl. No.: **86,820**

[22] Filed: **Jul. 2, 1993**

Related U.S. Application Data

[63] Continuation of Ser. No. 649,140, Jan. 30, 1991, Pat. No. 5,225,183, which is a continuation of Ser. No. 442,119, Nov. 28, 1989, abandoned.

[51] **Int. Cl.**[6] **A61L 9/04**

[52] **U.S. Cl.** **424/45**; 424/46; 424/451

[58] **Field of Search** 424/451, 45, 46

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Primary Examiner—Thurman K. Page
Assistant Examiner—Willaim E. Benston, Jr.
Attorney, Agent, or Firm—Gary L. Griswold; Walter N. Kirn; Douglas E. Reedich

[57] ABSTRACT

A self-propelling aerosol formulation which may be free from CFC's which comprises a medicament, 1,1,1,2-tetrafluoroethane, a surface active agent and at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane.

29 Claims, No Drawings

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MEDICINAL AEROSOL FORMULATIONS

This application is a continuation application of U.S. application Ser. No. 07/649,140 filed Jan. 30, 1991, now U.S. Pat. No. 5.225,183, which is a continuation of U.S. application Ser. No. 07/442,119 filed Nov. 28, 1989, now abandoned.

FIELD OF THE INVENTION

This invention relates to medicinal aerosol formulations and in particular to formulations suitable for pulmonary, nasal, buccal or topical administration which are at least substantially free of chlorofluorocarbons.

BACKGROUND TO THE INVENTION

Since the metered dose pressurised inhaler was introduced in the mid 1950's, inhalation has become the most widely used route for delivering bronchodilator drugs and steroids to the airways of asthmatic patients. Compared with oral administration of bronchodilators, inhalation offers a rapid onset of action and a low instance of systemic side effects. More recently, inhalation from a pressurised inhaler has been a route selected for the administration of other drugs, e.g., ergotamine, which are not primarily concerned with treatment of a bronchial malady.

The metered dose inhaler is dependent upon the propulsive force of a propellant system used in its manufacture. The propellant generally comprises a mixture of liquified chlorofluorocarbons (CFC's) which are selected to provide the desired vapour pressure and stability of the formulation. Propellants 11, 12 and 114 are the most widely used propellants in aerosol formulations for inhalation administration.

In recent years it has been established that CFC's react with the ozone layer around the earth and contribute towards its depletion. There has been considerable pressure around the world to reduce substantially the use of CFC's, and various Governments have banned the "nonessential" use of CFC's. Such "non-essential" uses include the use of CFC's as refrigerants and blowing agents, but heretofore the use of CFC's in medicines, which contributes to less than 1% of the total use of CFC's, has not been restricted. Nevertheless, in view of the adverse effect of CFC's on the ozone layer it is desirable to seek alternative propellant systems which are suitable for use in inhalation aerosols.

U.S. Pat. No. 4,174,295 discloses aerosol propellant compositions which consist of a mixture of a hydrogen-containing chlorofluorocarbon or fluorocarbon (A), selected from the group consisting of $CHClF_2$ (Freon 22), CH_2F_2 (Freon 32) and $CF_3—CH_3$ (Freon 143a), with a hydrogen-containing fluorocarbon or chlorofluorocarbon (B) selected from the group consisting of: CH_2ClF (Freon 31), $CClF_2—CHClF$ (Freon 123a), $CF_3—CHClF$ (Freon 124), $CHF_2—CClF_2$ (Freon 124a), $CHClF—CHF_2$ (Freon 133), $CF_3—CH_2Cl$ (Freon 133a), $CHF_2—CHF_2$ (Freon 134), $CF_3—CH_2F$ (Freon 134a), $CClF_2—CH_3$ (Freon 142b) and $CHF_2—CH_3$ (Freon 152a). The compositions may contain a third component (C) consisting of a saturated hydrocarbon propellant, e.g., n-butane, isobutane, pentane and isopentanes. The propellant compositions comprise 5 to 60% of (A), 5 to 95% of (B) and 0 to 50% of (C) and are said to be suitable for application in the fields of: hair lacquers, anti-perspiration products, perfumes, deodorants for rooms, paints, insecticides, for

home cleaning products, for waxes, etc. The compositions may contain dispersing agents and solvents, e.g., methylene chloride, ethanol etc.

It has now been found that 1,1,1,2-tetrafluoroethane has particularly suitable properties for use as a propellant for medicinal aerosol formulations when used in combination with a surface active agent and an adjuvant having a higher polarity than 1,1,1,2-tetrafluoroethane.

SUMMARY OF THE INVENTION

According to the present invention there is provided an aerosol formulation comprising a medicament, a surfactant, 1,1,1,2-tetrafluoroethane and at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane.

It has been found that 1,1,1,2-tetrafluoroethane, hereinafter referred to as Propellant 134a, may be employed as a propellant for aerosol formulations suitable for inhalation therapy when used in combination with a compound (hereinafter an "adjuvant") having a higher polarity than Propellant 134a. The adjuvant should be miscible with Propellant 134a in the amounts employed. Suitable adjuvants include alcohols such as ethyl alcohol, isopropyl alcohol, propylene glycol, hydrocarbons such as propane, butane, isobutane, pentane, isopentane, neopentane, and other propellants such as those commonly referred to as Propellants 11, 12, 114, 113, 142b, 152a 124, and dimethyl ether. The combination of one or more of such adjuvants with Propellant 134a provides a propellant system which has comparable properties to those of propellant systems based on CFC's, allowing use of known surfactants and additives in the pharmaceutical formulations and conventional valve components. This is particularly advantageous since the toxicity and use of such compounds in metered dose inhalers for drug delivery to the human lung is well established. Preferred adjuvants are liquids or gases at room temperature (22° C.) at atmospheric pressure.

Recently it has been established that certain CFC's which have been used as anaesthetics are not significantly ozone depleting agents as they are broken down in the lower atmosphere. Such compounds have a higher polarity than Propellant 134a and may be employed in the composition of the invention. Examples of such compounds include 2-bromo-2-chloro-1,1,1,-trifluoroethane, 2-chloro-1-(difluoromethoxy)-1,1,2-trifluroethane and 2-chloro-2-(difluromethoxy)-1,1,1-trifluoroethane.

In contrast to the prior art the compositions of the invention do not require the presence of Freon 22, Freon 32 or Freon 143a to provide useful properties; these propellants are preferably absent or present in minor amounts of less than 5% by weight of the propellant composition. The compositions are preferably free from CFC's.

The particular adjuvant(s) used and the concentration of the adjuvant(s) is selected according to the particular medicament used and the desired physical properties of the formulation.

It has been found that the use of Propellant 134a and drug as a binary mixture or in combination with a conventional surfactant such as sorbitan trioleate does not provide formulations having suitable properties for use with pressurised inhalers. It has been established that the physical parameters of polarity, vapour pressure, density, viscosity and interfacial tension are all important in obtaining a stable aerosol formulation, and by a

suitable selection of a compound having a polarity, higher than that of Propellant 134a stable aerosol formulations using Propellant 134a may be prepared.

The addition of a compound of higher polarity than Propellant 134a to Propellant 134a provides a mixture in which increased amounts of surfactant may be dissolved compared to their solubility in Propellant 134a alone. The presence of increased amounts of solubilised surfactant allows the preparation of stable, homogenous suspensions of drug particles. The presence of large amounts of solubilised surfactant may also assist in obtaining stable solution formulations of certain drugs.

The polarity of Propellant 134a and of an adjuvant may be quantified, and thus compared, in terms of a dielectric constant, or by using Maxwell's equation to relate dielectric constant to the square of the refractive index—the refractive index of materials being readily measurable or obtainable from the literature.

Alternatively, the polarity of adjuvants may be measured using the Kauri-butanol value for estimation of solvent power. The protocol is described in ASTM Standard: Designation 1133-86. However, the scope of the aforementioned test method is limited to hydrocarbon solvents having a boiling point over 40° C. The method has been modified as described below for application to more volatile substances such as is required for propellant.

Standardisation

In conventional testing the Kauri resin solution is standardised against toluene, which has an assigned value of 105, and a mixture of 75% n-heptane and 25% toluene by volume which has an assigned value of 40. When the sample has a Kauri-butanol value lower than 40, it is more appropriate to use a single reference standard of 75% n-heptane: 25% toluene. The concentration of Kauri-butanol solution is adjusted until a titre between 35 ml and 45 ml of the reference standard is obtained using the method of the ASTM standard.

Method for Volatile Compounds

The density of the volatile substance under test is calculated to allow a volumetric titration from the added weight of the sample after testing.

Kauri-butanol solution (20 g) is weighed into an aerosol bottle. A non-metering value is crimped onto the bottle and the weight of bottle and sample measured. Following the procedure detailed in ASTM standards as closely as possible, successive amounts of the volatile sample are transferred from an aerosol bottle via a transfer button until the end point is reached (as defined in ASTM). The aerosol bottle with titrated Kauri-butanol solution is re-weighed.

The Kauri-butanol value is calculated using the following formula:

$$V = \frac{(W_2 - W_1)}{d} \times \frac{40}{B}$$

in which:

W_2 = weight of aerosol bottle after titration (g)

W_1 = weight of aerosol bottle before titration (g)

d = density of sample (g/ml)

B is as defined in the ASTM standard and = ml of heptane-toluene blend required to titrate 20 g of Kauri-butanol solution.

If a titre (V) is obtained by precipitation of the Kauri resin out of solution, then a higher Kauri-butanol value represents a sample of higher polarity.

If the sample and Kauri-butanol solution are immiscible, this is most likely to be due to the immiscibility of the sample with butanol resulting from an excessively low polarity. However, it is feasible that excessively high polarity could result in immiscibility. This is tested by checking the miscibility of the sample with water. If the sample is immiscible with water and immiscible with Kauri-butanol solution, then the Kauri-butanol value is deemed too low to be measured, and the polarity is to be regarded as lower than that of any material which would give a proper titre into Kauri-butanol solution.

The particular selection of adjuvant and concentration preferably provides the resulting mixture with a solubility parameter of from 6.0 to 8.5 $(cal/cm^3)^{\frac{1}{2}}$. A propellant system having a solubility parameter below 6.0 $(cal/cm^3)^{\frac{1}{2}}$ is a poor solvent for surfactants, resulting in unstable suspension formulations of drug. The preferred solubility parameter for the propellant system comprising Propellant 134a and adjuvant is in the range 6.5 to 7.8 $(cal/cm^3)^{\frac{1}{2}}$.

The vapour pressure of a propellant system is an important factor as it provides the propulsive force for the medicament. The adjuvant is selected to moderate the vapour pressure of Propellant 134a so that it is within the desired range. This allows for advantages in the manufacture of the dosage form and gives greater flexibility to obtain and vary the target vapour pressure at room temperature. Another factor in the choice of the adjuvant is that, whilst it should allow moderation of the vapour pressure of Propellant 134a, it should not easily demix when the mixture is cooled to lower temperatures for the purposes of manufacture of the aerosol formulation and filling the containers.

The vapour pressure may also be increased if desired depending on the choice of the adjuvant. It has been found that some of the propellant mixtures deviate from Raoult's Law. The addition of certain alcohols makes very little change to the vapour pressure of the mixture with Propellant 134a at room temperature. However addition of certain hydrocarbons having a lower vapour pressure than Propellant 134a can result in a mixture having a higher vapour pressure.

The vapour pressure of the formulations at 25° C. is generally in the range 20 to 150 psig (1.4 to 10.3×10^5 N/m^2) preferably in the range 40 to 90 psig (2.8 to 6.2 $\times 10^5$ N/m^2).

The selection of adjuvant may also be used to modify the density of the formulation. Suitable control of the density may reduce the propensity for either sedimentation or "creaming" of the dispersed drug powders. The density of the formulations is generally in the range 0.5 to 2.0 g/cm^3 preferably in the range 0.8 to 1.8 g/cm^3, more preferably in the range 1.0 to 1.5 g/cm^3.

The selection of adjuvant may also be used to adjust the viscosity of the formulation which is desirably less than 10 cP.

The selection of adjuvant may also be used to adjust the interfacial tension of the propellant system. In order to optimise dispersion of drug particles and stability the interfacial tension of the formulation is desirably below 70 dynes/cm.

Propellant 134a is generally present in the aerosol formulations in an amount of at least 50% by weight of the formulation, normally 60 to 95% by weight of the formulation.

Propellant 134a and the component of higher polarity are generally employed in the weight ratio 50:50 to 99:1

Propellant 134a: high polarity component, preferably in the weight ratio 70:30 to 98:2 and more preferably in the weight ratio 85:15 to 95:5 Propellant 134a: high polarity component. Preferred compounds of higher polarity than Propellant 134a include ethanol, pentane, isopentane and neopentane.

The aerosol formulations comprise a surface active agent to stabilise the formulation and lubricate the valve components. Suitable surface active agents include both non-fluorinated surfactants and fluorinated surfactants known in the art and disclosed, for example, in British Patent Nos. 837465 and 994734 and U.S. Pat. No. 4,352,789. Examples of suitable surfactants include: oils derived from natural sources, such as, corn oil, olive oil, cotton seed oil and sunflower seed oil.

Sorbitan trioleate available under the trade name Span 85,

Sorbitan mono-oleate available under the trade name Span 80,

Sorbitan monolaurate available under the trade name Span 20,

Polyoxyethylene (20) sorbitan monolaurate available under the trade name Tween 20,

Polyoxyethylene (20) sorbitan mono-oleate available under the trade name Tween 80,

lecithins derived from natural sources such as those available under the trade name Epikuron particularly Epikuron 200.

Oleyl polyoxyethylene (2) ether available under the trade name Brij 92,

Stearyl polyoxyethylene (2) available under the trade name Brij 72,

Lauryl polyoxyethylene (4) ether available under the trade name Brij 30,

Oleyl polyoxyethylene (2) ether available under the trade name Genapol 0-020,

Block copolymers of oxyethylene and oxypropylene available under the trade name Synperonic,

Oleic acid, Synthetic lecithin, Diethylene glycol dioleate, Tetrahydrofurfuryl oleate, Ethyl oleate, Isopropyl myristate, Glyceryl trioleate, Glyceryl monolaurate, Glyceryl mono-oleate, Glyceryl monostearate, Glyceryl monoricinoleate, Cetyl alcohol, Stearyl alcohol, Polyethylene glycol 400, Cetyl pyridinium chloride.

The surface active agents are generally present in amounts not exceeding 5 percent by weight of the total formulation. They will usually be present in the weight ratio 1:100 to 10:1 surface active agent: drug(s), but the surface active agent may exceed this weight ratio in cases where the drug concentration in the formulation is very low.

Suitable solid medicaments include antiallergics, analgesics, bronchodilators, antihistamines,therapeutic proteins and peptides, antitussives, anginal preparations, antibiotics, anti-inflammatory preparations, hormones, or sulfonamides, such as, for example, a vasoconstrictive amine, an enzyme, an alkaloid, or asteroid, and synergistic combinations of these. Examples of medicaments which may be employed are: Isoproterenol [alpha-(isopropylaminomethyl) protocatechuyl alcohol], phenylephrine, phenylpropanolamine, glucagon, adrenochrome, trypsin, epinephrine, ephedrine, narcotine, codeine, atropine, heparin, morphine, dihydromorphinone, ergotamine, scopolamine, methapyrilene, cyanocobalamin, terbutaline, rimiterol, salbutamol, flunisolide, colchicine, pirbuterol, beclomethasone, orciprenaline, fentanyl, and diamorphine. Others are antibiotics, such as neomycin, streptomycin, penicillin, procaine penicillin, tetracycline, chlorotetracycline and hydroxytetracycline; adrenocorticotropic hormone and adrenocortical hormones, such as cortisone, hydrocortisone, hydrocortisone acetate and prednisolone; insulin, antiallergy compounds such as cromolyn sodium, etc.

The drugs exemplified above may be used as either the free base or as one or more salts known to the art. The choice of free base or salt will be influenced by the physical stability of the drug in the formulation. For example, it has been shown that the free base of salbutamol exhibits a greater dispersion stability than salbutamol sulphate in the formulations of the invention.

The following salts of the drugs mentioned above may be used; acetate, benzenesulphonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, fluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulphate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulphate, tannate, tartrate, and triethiodide.

Cationic salts may also be used. Suitable cationic salts include the alkali metals, e.g. sodium and potassium, and ammonium salts and salts of amines known in the art to be pharmaceutically acceptable, e.g. glycine, ethylene diamine, choline, diethanolamine, triethanolamine, octadecylamine, diethylamine, triethylamine, 1-amino-2-propanol-amino-2-(hydroxymethyl)propane-1,3-diol and 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol.

For pharmaceutical purposes the particle size of the powder should desirably be no greater than 100 microns diameter, since larger particles may clog the valve or orifice of the container. Preferably the particle size should be less than 25 microns in diameter. Desirably the particle size of the finely-divided solid powder should for physiological reasons be less than 25 microns and preferably less than about 10 microns in diameter. The particle size of the powder for inhalation therapy should preferably be in the range 2 to 10 microns.

There is no lower limit on particle size except that imposed by the use to which the aerosol produced is to be put. Where the powder is a solid medicament, the lower limit of particle size is that which will be readily absorbed and retained on or in body tissues. When particles of less than about one-half micron in diameter are administered by inhalation they tend to be exhaled by the patient.

The concentration of medicament depends upon the desired dosage but is generally in the range 0.01 to 5% by weight.

The formulation of the invention may be filled into conventional aerosol containers equipped with metering valves and dispensed in an identical manner to formulations employing CFC's.

The invention will now be illustrated by the following Examples. The following components were used in the Examples:

Salbutamol Sulphate B.P., micronised—Salbutamol

Beclomethasone Dipropionate Isopropylacohol solvate, micronised—BDP

Sodium Cromoglycate B.P., micronised—DSCG

Sorbitan trioleate—Span 85

Lecithin commercially available under the trade name Lipoid S100 —Lipoid S100
Oleic Acid B.P.—oleic acid
1,1,1,2-Tetrafluoroethane—P134a
Ethyl alcohol B.P.—ethanol n-Pentane, standard laboratory reagent—n—pentane The formulations in the Examples were prepared by the following techniques.

Each drug and surfactant combination was weighed into a small beaker. The required quantity of the higher boiling point component of the propellant system e.g. ethanol was added and the mixture homogenised using a Silverson mixer. The required quanity of the mixture was dispensed into a P.E.T. bottle and an aerosol valve crimped in place. Propellant 134a was added to the required weight by pressure filling.

EXAMPLES 1 to 6

Formulations Containing Salbutamol

The formulations reported in the following Tables were prepared.

Ingredient (g)	Example No. 1	2	3
Salbutamol	0.010	0.010	0.010
Span 85	0.012	—	—
Oleic Acid	—	0.012	—
Lipoid S100	—	—	0.012
n-Pentane	1.240	1.240	1.240
P134a	3.720	3.720	3.720

Ingredient (g)	Example No. 4	5	6
Salbutamol	0.010	0.010	0.010
Span 85	0.012	—	—
Oleic Acid	—	0.012	—
Lipoid S100	—	—	0.012
Ethanol	1.350	1.350	1.350
P134a	4.040	4.040	4.040

All formulations comprised a suspension of salbutamol. Examples 4 to 6 containing ethanol appeared to be more stable than Examples 1 to 3 containing n-pentane, exhibiting a decreased tendency to settling.

EXAMPLES 7 to 12

Formulations containing Beclomethasone Dipropionate

The formulations reported in the following Tables were prepared.

Ingredient (g)	Example No. 7	8	9
BDP	0.005	0.005	0.005
Span 85	0.012	—	—
Oleic Acid	—	0.012	—
Lipoid S100	—	—	0.006
n-Pentane	1.240	1.240	1.240
P134a	3.720	3.720	3.720

Ingredient (g)	Example No. 10	11	12
BDP	0.005	0.005	0.005
Span 85	0.006	—	—
Oleic Acid	—	0.006	—
Lipoid S100	—	—	0.006
Ethanol	1.350	1.350	1.350
P134a	4.040	4.040	4.040

For those formulations containing n-pentane, Examples 7 and 8 appeared less turbid than Example 9, and Example 8 appeared to form a solution after 4–5 days.

Examples 10 to 12 produced solution formulations.

EXAMPLES 13 to 18

Formulations Containing Sodium Cromoglycate

The formulations reported in the following Tables were prepared.

Ingredient (g)	Example No. 13	14	15
DSCG	0.100	0.100	0.100
Span 85	0.024	—	—
Oleic Acid	—	0.024	—
Lipoid S100	—	—	0.024
n-Pentane	1.240	1.240	1.240
P134a	3.720	3.720	3.720

Ingredient (g)	Example No. 16	17	18
DSCG	0.100	0.100	0.100
Span 85	0.006	—	—
Oleic Acid	—	0.006	—
Lipoid S100	—	—	0.006
Ethanol	1.350	1.350	1.350
P134a	4.040	4.040	4.040

Examples 13 to 18 produced suspension formulations, Examples 16 to 18 containing ethanol exhibiting better stability properties than Examples 13 to 15 containing n-pentane.

EXAMPLES 19 to 23

The following Examples illustrate the use of different adjuvants with Propellant 134a.

Ingredient (g)	Example No. 19	20	21	22	23
Salbutamol	0.012	0.012	0.012	0.012	—
BDP	—	—	—	—	0.010
Span 85	0.001	0.001	0.001	0.001	—
Oleic Acid	—	—	—	—	0.001
P134a	4.98	5.22	5.28	5.61	5.04
neopentane	0.55	—	—	—	—
Isopropyl-alcohol	—	0.58	—	—	
Isopropyl-myristate	—	—	0.59	—	—
Propellant 11	—	—	—	0.62	—
Isopentane	—	—	—	—	0.56

Each Example was 5 ml in volume and was in the form of a stable suspension.

EXAMPLE 24

This Example illustrates the use of different surfactants in the following basic formulations:

Salbutamol	0.012 g
Ethanol	0.58 g
P134a	5.220 g
Surfactant	A or B

Volume = 5 ml
A = 0.005 g
B = 0.012 g

The following surfactants were employed to form stable suspensions in the concentrations specified.

1.	Span 85	A, B.	16.	Isopropyl myristate	B.
2.	Span 80	A.	17.	Glyceryl trioleate	A, B.
3.	Span 20	A.	18.	Glyceryl monolaurate	A.
4.	Tween 20	A.	19.	Glyceryl mono-oleate	A.
5.	Tween 80	A.	20.	Glyceryl monostearate	A.
6.	Oleic acid	A, B.	21.	Glyceryl monoricinoleate	A.
7.	Epikuron 200	B.	22.	Cetyl alcohol	A.
8.	Synthetic lecithin	B.	23.	Stearyl alcohol	B.
9.	Brij 92	A.	24.	Polyethylene glycol 400	B.
10.	Brij 72	A.	25.	Synperonic PE L61	A.
11.	Brij 30	B.	26.	Synperonic PE L64	A.
12.	Genapol 0-020	A.	27.	Synperonic PE L92	A.
13.	Diethylene glycol dioleate	A.	28.	Synperonic PE P94	A.
14.	Tetrahydrofurfuryl oleate	A.	29.	Cetyl pyridinium chloride	A.
15.	Ethyl oleate	A.	30.	FC 807 free acids (consisting mainly of bis(perfluoro-n-octyl-N-ethyl sulphonamidoethyl) phosphate)	A, B.
			31.	Corn Oil	B.

We claim:

1. An aerosol formulation comprising: a medicament, a propellant comprising 1,1,1,2-tetrafluoroethane and less than 5% by weight of $CHClF_2$, CH_2F_2, CF_3CH_3, or a mixture thereof, a surface active agent, and at least one other compound having a higher polarity than 1,1,1,2-tetrafluoroethane according to the Kauri-butanol value.

2. An aerosol formulation according to claim 1, wherein the compound of higher polarity is selected from the group consisting of ethyl alcohol, isopropyl alcohol, propylene glycol, propane, butane, isobutane, pentane, isopentane, neopentane, Propellants 11, 12, 114, 113, 142b, 152a, and 124, and dimethyl ether.

3. An aerosol formulation according to claim 1, suitable for administration to a patient by oral or nasal inhalation.

4. An aerosol formulation according to claim 3, wherein the drug is present in the form of particles having a median particle size of less than 10 microns.

5. An aerosol formulation according to claim 3, wherein the drug is in solution.

6. An aerosol formulation according to claim 3, wherein 1,1,1,2-tetrafluoroethane is present in an amount of at least 50% by weight of the formulation.

7. An aerosol formulation according to claim 3, wherein the 1,1,1,2-tetrafluoroethane is present in an amount between 60% and 95% by weight of the formulation.

8. An aerosol formulation according to claim 3, wherein the ratio of the weight of 1,1,1,2-tetrafluoroethane to the weight of compound of higher polarity is in the range 1:1 to 99:1.

9. An aerosol formulation according to claim 3, wherein the ratio of the weight of 1,1,1,2-tetrafluoroethane to the weight of compound of higher polarity is in the range 2.33:1 to 49:1.

10. An aerosol formulation according to claim 3, wherein the ratio of the weight of 1,1,1,2-tetrafluoroethane to the weight of compound of higher polarity is in the range 5.67:1 to 19:1.

11. An aerosol formulation according to claim 3, wherein the surface active agent is selected from the group consisting of sorbitan trioleate, sorbitan monooleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monooleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, oleic acid, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol 400 and cetyl pyridinium chloride, olive oil, glyceryl monolaurate, corn oil, cotton seed oil and sunflower seed oil.

12. An aerosol formulation according to claim 3, wherein the ratio of the weight of surface active agent to weight of medicament is in the range 1:100 to 10:1 .

13. An aerosol formulation according to claim 3, wherein the medicament is selected from the group consisting of salbutamol, beclomethasone dipropionate, disodium cromoglycate, pirbuterol, isoprenaline, adrenaline, rimiterol, and ipratroprium bromide.

14. An aerosol formulation according to claim 3, wherein the medicament is present in an amount of 0.01% to 5% by weight of the formulation.

15. An aerosol formulation comprising a medicament, a propellant comprising 1,1,1,2-tetrafluoroethane, a surface active agent, and at least one other compound having a higher polarity than 1,1,1,2-tetrafluoroethane according to Kauri-butanol value, the formulation being free of chlorofluorocarbons.

16. An aerosol formulation according to claim 15, wherein the compound of higher polarity is selected from the group consisting of ethyl alcohol, isopropyl alcohol, propylene glycol, propane, butane, isobutane, pentane, isopentane, neopentane, and dimethyl ether.

17. An aerosol formulation according to claim 15 suitable for administration to a patient by oral or nasal inhalation.

18. An aerosol formulation according to claim 15, wherein the drug is present in the form of particles having a median particle size of less than 10 microns.

19. An aerosol formulation according to claim 15, wherein the drug is in solution.

20. An aerosol formulation according to claim 15, wherein 1,1,1,2-tetrafluoroethane is present in an amount of at least 50% by weight of the formulation.

21. An aerosol formulation according to claim 15, wherein the 1,1,1,2-tetrafluoroethane is present in an amount between 60% and 95% by weight of the formulation.

22. An aerosol formulation according to claim 15, wherein the ratio of the weight of 1,1,1,2-tetrafluoroethane to the weight of compound of higher polarity is in the range 1:1 to 99:1.

23. An aerosol formulation according to claim 15, wherein the ratio of the weight of 1,1,1,2-tetrafluoroethane to the weight of compound of higher polarity is in the range 2.33:1 to 49:1.

24. An aerosol formulation according to claim 15, wherein the ratio of the weight of 1,1,1,2-tetrafluoroethane to the weight of compound of higher polarity is in the range 5.67:1 to 19:1.

25. An aerosol formulation according to claim 15, wherein the surface active agent is selected from the group consisting of sorbitan trioleate, sorbitan monooleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monooleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, oleic acid, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol 400 and cetyl pyridinium chloride, olive oil, glyceryl monolaurate, corn oil, cotton seed oil and sunflower seed oil.

26. An aerosol formulation according to claim 15, wherein the ratio of the weight of surface active agent to weight of medicament is in the range 1:100 to 10:1.

27. An aerosol formulation according to claim 15, wherein the medicament is selected from the group consisting of salbutamol, beclomethasone dipropionate, disodium cromoglycate, pirbuterol, isoprenaline, adrenaline, rimiterol, and ipratroprium bromide.

28. An aerosol formulation according to claim 15, wherein the medicament is present in an amount of 0.01% to 5% by weight of the formulation.

29. An aerosol formulation comprising: a medicament, a propellant comprising 1,1,1,2-tetrafluoroethane and less than 5% by weight of $CHClF_2$, CH_2F_2, CF_3CH_3, or a mixture thereof, a surface active agent, and isopropyl myristate.

* * * * *

EXHIBIT D

PATENT

Docket No. 43853USA1D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Examiner: W. Benston, Jr.
TARLOCHAN S. PUREWAL AND DAVID J. GREENLEAF	Group Art Unit: 1502
Serial No.: 08/086,820	
Filed: July 2, 1993	DUE DATE(S) _____
For: MEDICINAL AEROSOL FORMULATIONS	ATTORNEY DOCKETED

TERMINAL DISCLAIMER UNDER 37 C.F.R. 1.321(b)

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Petitioner, Riker Laboratories, Inc., a corporation of the State of Delaware having a place of business at 3M Center, St. Paul, Minnesota, hereby represents that it is the exclusive owner of the entire interest in the above-identified Application, by virtue of an assignment recorded at Reel 5187, Frame 598-600, on November 28, 1989. Petitioner further represents that it is the exclusive owner of the entire interest in U.S. Patent No. 5,225,183, by virtue of an assignment recorded at Reel 5187, Frame 598-600, on November 28, 1989.

Petitioner hereby disclaims the terminal part of any patent granted on the above-identified Application which would extend beyond November 28, 2006, the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the above-identified patent, not shortened by terminal disclaimer. Petitioner hereby agrees that any patent granted on the above-identified Application shall be enforceable only for and during such period that the legal title to such patent and U.S. Patent No. 5,225,183 are commonly owned. This agreement is to run with any patent granted on the above-identified application and to be binding upon the grantee, its successor, or assigns.

In making the above disclaimer, Petitioner does not disclaim any terminal part of any patent granted on the above-identified Application prior to the expiration date of the full statutory term, not shortened by terminal disclaimer, of U.S. Patent No. 5,225,183, if it: (1) expires for failure to pay a maintenance fee; (2) is held unenforceable or is found invalid by a court of competent jurisdiction; (3) is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321; (4) has all claims canceled by a reexamination certificate; (5) is reissued; or (6) is otherwise terminated prior to the expiration of its full statutory term.

The undersigned (whose title is supplied below) is empowered to act on behalf of Petitioner.

Documents establishing the chain of title of the subject patent (including the aforementioned assignment and a recording location) have been reviewed and I certify that, to the best of my knowledge and belief, title is in Petitioner.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

A check in the amount of $110.00 for the fee required by 37 C.F.R. 1.20(d) is submitted herewith. Please charge any additional fees or credit any overpayment to Deposit Account No. 13-3723.

RIKER LABORATORIES, INC.

W. George Meredith
Vice President and
General Manager

Date: November 16, 1994

DER/mlh
43853-1D.TER

EXHIBIT E

Patent
Docket No.: 43853USA1D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: TARLOCHAN S. PUREWAL AND DAVID J. GREENLEAF	**Certificate Of Corrections Branch**
Serial No.: 08/086,820 U.S. Patent 5,439,670 Issued: August 8, 1995 For: MEDICINAL AEROSOL FORMULATIONS	Group Art Unit: 1502 Examiner: W. Benston, Jr.

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 C.F.R. 1.322

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

It is respectfully requested that a Certificate of Correction be issued in connection with the subject patent in accordance with the provisions of 37 C.F.R. 1.322 and Patent Office Notice dated January 24, 1975.

The required text is submitted in duplicate.

In the transmittal of application serial number 08/086,820 mailed July 2, 1993, we referred to the power of attorney of record in prior application 067/649,140 filed on January 30, 1991. Within this power of attorney foreign priority was claimed. Because the listed errors first occurred in the printed patent, and thus are not due to Applicant's mistake, no fee is required in connection with this Certificate.

October 10, 1996

Respectfully Submitted By:

Walter N. Kirn
Registration No. 21,196

3M Office of Intellectual Property Counsel
P.O. Box 33427
St. Paul, Minnesota 55133-3427
Telephone: (612) 733-1523
Facsimile: (612) 736-3833

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.: 5,439,670

DATED: August 8, 1995

INVENTOR(S): Tarlochan S. Purewal and David J. Greenleaf

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page, insert item [30], -- Foreign Application Priority Data, December 6, 1988 [GB] United Kingdom 8828477.3 --.

Column 5, line 58, "asteroid" should read -- a steroid -- .

MAILING ADDRESS OF SENDER:

MINNESOTA MINING AND MANUFACTURING COMPANY
OFFICE OF INTELLECTUAL PROPERTY COUNSEL
3M CENTER - P.O. BOX 33427
SAINT PAUL, MINNESOTA 55133-3427

PATENT NO. 5,439,670

No. of add'l copies
@ 50¢ per page

EXHIBIT F

CERTIFICATION

I hereby certify that this is an original copy of Application for Patent Extension of U.S. Patent No. 5,439,670.

Date: October 10, 1996

Walter N. Kirn
Registration No. 21,196

State of Minnesota)
) ss
County of Ramsey)

On this 10th day of October, 1996, before me personally appeared the above-named Walter N. Kirn personally known to me, and known by me to be the person described in and who executed the foregoing instrument, and who acknowledged that he executed the same as his free act and deed, on the day and year aforesaid.

MARY L. HOFF
NOTARY PUBLIC - MINNESOTA
WASHINGTON COUNTY
My Comm. Expires Jan. 31, 2000

Notary Public

Office of
Intellectual Property Counsel

3M

October 10, 1996

Honorable Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Included herewith is an Application for Patent Extension (Attorney's Docket No. F.N. 43853USA1D) of the term of U.S. Patent No. 5,439,670 being filed by Riker Laboratories, Inc. This Application includes an original copy of the Application itself (including the Declaration and Power of Attorney).
Please charge the filing fee of $1090.00 to Deposit Account No. 13-3723. Please charge to Deposit Account No. 13-3723 any additional fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of this application. This authorization includes the fee for any extension of time under 37 CFR 1.136(a) that may be necessary. To the extent any such extension should become necessary it is hereby requested.

Respectfully submitted,

Walter N. Kirn
Registration No. 21,196

TKR\mlh
P:\FEULNGRE\PTE\PATEXTEN.LTR

Minnesota Mining and
Manufacturing Company

PO Box 33427
St. Paul, MN 55133-3427 USA
612 733 1500
612 736 3833 Facsimile
29 7023 Telex
PATENTS Cable

Office of
Intellectual Property Counsel

3M

October 10, 1996

Honorable Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Included herewith is an Application for Patent Extension (Attorney's Docket No. F.N. 43853USA1D) of the term of U.S. Patent No. 5,439,670 being filed by Riker Laboratories, Inc. This Application includes an original copy of the Application itself (including the Declaration and Power of Attorney).
Please charge the filing fee of $1090.00 to Deposit Account No. 13-3723. Please charge to Deposit Account No. 13-3723 any additional fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of this application. This authorization includes the fee for any extension of time under 37 CFR 1.136(a) that may be necessary. To the extent any such extension should become necessary it is hereby requested.

Respectfully submitted,

Walter N. Kirn
Registration No. 21,196

TKR\mlh
P:\FEULNGRE\PTE\PATEXTEN.LTR

Minnesota Mining and
Manufacturing Company

PO Box 33427
St. Paul, MN 55133-3427 USA
612 733 1500
612 736 3833 Facsimile
29 7023 Telex
PATENTS Cable

CERTIFICATION

I hereby certify that this is an original copy of Application for Patent Extension of U.S. Patent No. 5,439,670.

Date: October 10, 1996

Walter N. Kirn
Registration No. 21,196

State of Minnesota)
) ss
County of Ramsey)

On this 10th day of October, 1996, before me personally appeared the above-named Walter N. Kirn personally known to me, and known by me to be the person described in and who executed the foregoing instrument, and who acknowledged that he executed the same as his free act and deed, on the day and year aforesaid.

Notary Public